water-soluble luminescent semiconductor quantum dot remains in solution for at least about one day. The present invention further provides a composition comprising the water-soluble luminescent semiconductor quantum dot and a method of obtaining a water-soluble luminescent semiconductor quantum dot.

The Pending Claims

Claims 1-23 and 38-39 are pending currently. Claims 1-20 are directed to the water-soluble luminescent semiconductor quantum dot. Claims 21-23 are directed to the composition, and claims 38-39 are directed to the method of obtaining a water-soluble luminescent semiconductor quantum dot. Reconsideration of the pending claims is respectfully requested.

The Amendments to the Claims

Claims 24-37 and 40-68 have been canceled without prejudice as being directed to non-elected inventions. Applicants expressly reserve the right to pursue the canceled claims in a divisional application. In addition, claim 1 has been amended to recite that the water-soluble luminescent semiconductor quantum dot remains in solution for at least about one day. The amendment to claim 1 is supported by the specification at, for example, page 4, lines 28-30. No new matter has been added by way of this amendment. Separate documents setting forth the precise changes to the claims as well as the text of all of the pending claims are enclosed herewith.

Summary of the Office Action

The Office Action rejects claims 1-6, 9-14, 17-18, 21, and 38-39 under Section 102(e), as allegedly being anticipated by U.S. Patent 5,990,479 (Weiss et al.). Claims 7-8 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious in view of Weiss et al., taken in view of Lawless et al. (*Journal of Physical Chemistry*, *99*, 10329 (1995)). Claims 15-16 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious in view of Weiss et al., taken in view of Hines et al. (*Journal of Physical Chemistry*, *100*(2), 468 (1996)). Claims 19-20 and 22-23 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious in view of Weiss et al, taken in view of Hines et al. and Lawless et al.

Discussion of Anticipation Rejection

Claims 1-6, 9-14, 17-18, 21, and 38-39 are rejected under 35 U.S.C. § 102(e), as allegedly being anticipated by U.S. Patent 5,990,479 (Weiss et al.). According to the Office, Weiss et al. discloses the use of water soluble quantum dots as probes for biological application wherein the quantum dot is linked to an affinity molecule. The quantum dots allegedly comprise a semiconductor nanocrystal and a shell of another semiconductor nanocrystal material. The quantum dot allegedly is linked to an affinity molecule via a ligand that contains a hydrophobic region and a hydrophilic region. As such, the Office contends that Weiss et al. anticipates claims 1-6, 9-14, 17-18, 21, and 38-39. This rejection is respectfully traversed for the reasons set forth below.

The present invention is directed, in part, to a water-soluble luminescent semiconductor quantum dot comprising a core, a cap, and a hydrophilic attachment group. The water-soluble luminescent semiconductor quantum dot remains in solution for at least about one day. The ability of the present inventive quantum dots to remain in solution for extended periods of time is advantageous for biological applications. Luminescent semiconductor quantum dots that quickly precipitate out of solution are not suitable for detecting target molecules in biological samples. There is no teaching or suggestion in Weiss et al. that the nanocrystal compounds disclosed therein are water-soluble, much less able to remain in solution for at least about one day. Moreover, the semiconductor nanocrystal compounds disclosed by Weiss et al. are substantially dissimilar to those of the present invention. For example, Weiss et al. discloses nanocrystal compounds which are coated with a thin layer of glass, such as silica glass, and further attached to a linking agent (Weiss et al., column 7, line 8, through column 8, line 60). Such nanocrystal compounds are chemically distinct from the present inventive water-soluble luminescent semiconductor quantum dots due to the glass coating.

The linking agents disclosed in Weiss et al. at, for instance, column 8, lines 15-45, while perhaps comprising a hydrophilic group, do not enable the nanocrystal compound to remain in solution for at least one day. For example, in Example 1A of the instant application, Applicants constructed the nanocrystal compound described in Example 1 of Weiss et al. As set forth in the instant Example 1A, the nanocrystal compound of Weiss et al. precipitated out of solution after one hour, an indication of the instability of the disclosed nanocrystal compounds. In addition, Applicants have sought to construct a nanocrystal compound as described in Example 2 of Weiss et al. As established in the accompanying Declaration under 35 C.F.R. § 1.132, executed by Dr. Shuming Nie, the 3-

mercaptopropyl-trimethoxy silane linker of the nanocrystal compounds described in Example 2 of Weiss et al. polymerizes and crosslinks to form an insoluble gel in water shortly after construction. As set forth by Dr. Nie, the formed nanoparticles of Example 2 of Weiss et al. are not considered as being in "solution," as that term is used in the art. Thus, the disclosed nanocrystal compounds of Weiss et al. do not remain in solution for at least about one day, as required by the present invention as recited in claim 1. Thus, claim 1 (and all claims dependent thereon) are not anticipated by Weiss et al.

Furthermore, claims 1-6, 9-14, 17-18, and 21 cannot be considered as obvious in view of Weiss et al. There is no teaching or suggestion in Weiss et al. of water-soluble luminescent semiconductor quantum dots, which comprise a core, a cap, and a hydrophilic attachment group and that remain in solution for at least about one day. There is no pointer in Weiss et al. that such nanoparticles can be generated, or that such nanoparticles are particularly advantageous for use in biological assays. As such, claims 1-6, 9-14, 17-18, 21 are clearly non-obvious in view of Weiss et al.

With respect to pending claims 38 and 39, the present invention provides a method of obtaining a water-soluble luminescent semiconductor quantum dot. The method comprises reacting a luminescent semiconductor quantum dot in a nonpolar organic solvent with a first aqueous solution comprising an attachment group. A second aqueous solution of about neutral pH is added and the reaction is mixed. Finally, an aqueous layer is extracted, thereby obtaining a water-soluble luminescent semiconductor quantum dot. The methods of making nanocrystal compounds disclosed by Weiss et al. do not comprise adding a second aqueous solution of about neutral pH (see Weiss et al. at, for instance, Examples 1 and 2). The addition of a second aqueous solution of about neutral pH to the reaction is not so much as suggested by the cited reference. Thus, Weiss et al. does not disclose the present inventive method of obtaining a water-soluble luminescent semiconductor quantum dot. In preparing water-soluble luminescent semiconductor quantum dots for conjugation to a biomolecule, the present inventive method of obtaining a water-soluble luminescent semiconductor quantum dot is superior to that described in Weiss et al., in that Weiss et al. requires an additional step in the method. The necessity of additional steps requires more laboratory time and likely results in reduced sample yield.

In view of the above, the present invention is clearly novel and non-obvious over the cited art, and Applicants respectfully request withdrawal of the rejection.

Discussion of Obviousness Rejection

Claims 7-8 are rejected under Section 103(a) as allegedly being obvious in view of Weiss et al, taken in view of Lawless et al. Claims 15-16 are rejected under Section 103(a) as allegedly being obvious in view of Weiss et al., taken in view of Hines et al. Finally, claims 19-20 and 22-23 are rejected under Section 103(a) as allegedly being obvious in view of Weiss et al., taken in view of Hines et al. and Lawless et al. These rejections are believed to be overcome for the reasons discussed above and also for the reasons set forth below.

The disclosure of Weiss et al. is discussed above. Briefly, Weiss et al. does not teach or suggest a water-soluble luminescent semiconductor quantum dot comprising a core, a cap, and a hydrophilic attachment group, wherein the water-soluble luminescent semiconductor quantum dot remains in solution for at least about one day. The nanocrystal compounds disclosed by Weiss et al. are not sufficiently water-soluble so as to be suitable for biological applications.

Lawless et al. is directed to capping of CdS nanoparticles with mercaptocarboxylic acid as a method of controlling size of the particle and further linking the nanoparticle to TiO_2. The Office contends that it would have been obvious to one of ordinary skill in the art to use mercaptoacetic acids as a linking agent in the quantum dot of Weiss et al. because mercaptopropionic acid has the advantage of being able to efficiently control the size of the quantum dot to exhibit a more uniform emission spectrum. However, one of ordinary skill in the art would not have combined the disclosures of Weiss et al. and Lawless et al. to obtain a water-soluble luminescent semiconductor quantum dot. First, the nanocrystal compounds of Weiss et al. and Lawless et al. are created using different procedures. In the art, one of ordinary skill would not necessarily believe that the linkers described in Lawless et al. would be appropriate for the nanocrystal compounds of Weiss et al.

Second, the nanocrystals of Lawless et al. do not comprise a semiconductor cap. The linkers of Lawless et al. are attached to the nanoparticle core and used to link the nanoparticle to TiO_2. There is no suggestion in Lawless et al. to attach a linker to semiconductor-capped nanocrystal. Furthermore, there is no teaching or suggestion in Lawless et al. to use the nanoparticles described in any biological applications, as is the focus of Weiss et al. The linkers of Lawless et al. are employed to control particle size and to link the nanoparticle core to another metal compound. The linkers described in Weiss et al. are employed to attach the nanocrystal compound to a biological molecule.

Thus, one of ordinary skill in the art would not have combined the disclosures of Weiss et al. and Lawless et al.

Finally, if attempting to create a water-soluble luminescent semiconductor quantum dot, the ordinarily skilled artisan would not have believed that the linkers of Lawless et al. would have rendered a quantum dot water-soluble based on the disclosure of Weiss et al. Weiss et al. disclose nanocrystal compounds comprising (4-mercapto)benzoic acid and 3-mercaptopropyl-trimethoxy silane as linkers. The disclosed linkers do not render the nanocrystal water-soluble, wherein the nanocrystal remains in solution for at least about one day. Therefore, Weiss et al. discloses a class of mercaptocarboxylic acids that are not suitable for the quantum dots of the present invention. Upon review of Weiss et al., one of ordinary skill in the art would not assume that the mercaptocarboxylic acids of Lawless et al. would render a nanoparticle water-soluble, as required by the pending claims. Thus, the ordinarily skilled artisan would be not have been motivated to combine the cited references as contended by the Office.

The Office contends that Hines et al. discloses ZnS-capped CdSe nanocrystals, and has rejected claims 15-16 as allegedly being obvious over Weiss et al., in view of Hines et al. In particular, the Office contends that it would have been obvious to the ordinarily skilled artisan to use the ZnS-CdSe nanoparticles of Hines et al. in the nanocrystal compound of Weiss et al. However, Hines et al. does not cure the deficiencies of Weiss et al. Weiss et al. does not teach or suggest a water-soluble luminescent semiconductor quantum dot that remains in solution for at least about one day, as discussed above. One of ordinary skill in the art still would not arrive at the present invention by combining the references as suggested by the Office. As such, claims 15-16 cannot be considered as obvious over Weiss et al., taken in view of Hines et al.

Finally, the Office has rejected claims 19-20 and 22-23 as allegedly being obvious in view of Weiss et al., taken in view of Lawless et al. and Hines et al. However, as set forth above, the disclosures of Weiss et al., Lawless et al., and Hines et al. cannot be combined as alleged by the Office to arrive at the invention of claims 19-20 and 22-23. Weiss et al. does not teach or suggest a water-soluble luminescent semiconductor quantum dot comprising a core, a cap, and a hydrophilic attachment group, wherein the water-soluble luminescent semiconductor quantum dot remains in solution for at least about one day. While Lawless et al. may describe the attachment of mercaptocarboxylic acids to nanoparticles, the nanoparticles of Lawless et al. are not capped, and there is no teaching or suggestion in Lawless et al. to construct water-soluble nanoparticles.

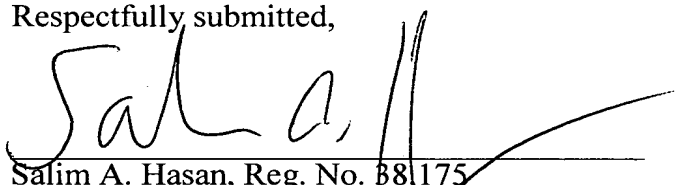
Moreover, one of ordinary skill in the art would not have believed the linkers of Lawless et al. would render a nanoparticle water-soluble in view of the teaching of Weiss et al., which discloses mercaptocarboxylic acid linkers that cause precipitation of the nanoparticle prior to about one day. Thus, one of ordinary skill in the art would not have been motivated to combine the teachings of Weiss et al. and Lawless et al. Furthermore, Hines et al. does not cure the deficiencies of Weiss et al. and Lawless et al. Hines et al. allegedly merely discloses ZnS-CdSe nanoparticles, with no teaching or suggestion of attachment groups or the possibility of obtaining water-soluble nanoparticles. Thus, the subject matter of claims 19-20 and 22-23 cannot be considered as obvious over the prior art.

In view of the above, Applicants submit that the subject matter of claims 7-8, 15-16, 19-20, and 22-23 is novel and unobvious in view of the cited art. Accordingly, withdrawal of the rejection under Section 103(a) is requested.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: February 20, 2001

In re Appln. of Nie et al.
Application No. 09/405,653

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CERTIFICATE OF MAILING

I hereby certify that this AMENDMENT (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

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In re Application of:

Nie et al.

Group Art Unit: 1765

Application No. 09/405,653

Examiner: Unassigned

Filed: September 24, 1999

For: WATER-SOLUBLE LUMINESCENT QUANTUM DOTS AND BIOMOLECULAR CONJUGATES THEREOF AND RELATED COMPOSITIONS AND METHOD OF USE

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FEB 27 2001
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AMENDMENTS TO CLAIMS ON FEBRUARY 19, 2001

1. (Amended) A water-soluble luminescent semiconductor quantum dot, which comprises a core, a cap and a hydrophilic attachment group, wherein the water-soluble luminescent semiconductor quantum dot remains in solution for at least about one day.